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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Howard K. Shapiro Docket: P-1018

Application No.: 09/194,619 Art Unit: 1649

Filed: 25 August 2003 Examiner: Daniel E. Kolker, Ph.D.

For: Methods and Compositions for Development of Drug Screening Procedures and Diagnostic Tools

RESPONSE TO RESTRICTION REQUIREMENT

To the Commissioner of Patents and Trademarks:

This communication is in response to the USPTO letter with mailing date of 21 July 2005 as issued by Daniel E. Kolker, Ph.D., confirmation no. 3413.

The examiner's letter is a restriction requirement, as noted in point (1) of the USPTO letter. In point (2) of the USPTO letter, the examiner cited the prior art of May and Gray (1985) as grounds for asserting that "there is not a special technical feature which links all inventions." The applicant respectfully disagrees with the examiner's citation of May and Gray (1985) on the following grounds.

The inventor states now, as he has enumerated in his claims as filed, that the claims relate to and depend upon the detection of "stress protein expression" and use thereof to identify drug candidate agents that preferentially suppress stress protein expression in fibroblasts derived from a patient having a pre-determined neurological disease, while not suppressing stress protein expression in fibroblasts derived from a control fibroblast donor [see Claim 1 (d)]. Some chemical substances might generally suppress stress protein expression, now described by the applicant as "false hits." These chemical substances are regarded by the applicant as being of no practical value as drug candidate agents of possible use in clinical treatment of the neurological disease. So, Claim 1 is formatted so as to provide data that makes a clear distinction between chemical substances that are "false hits" and drug candidate agents that preferentially suppress stress protein expression in fibroblasts derived from a patient having a pre-determined neurological disease.

Nowhere in May and Gray (1985) is the instant invention disclosed or anticipated. May and Gray (1985) used human fibroblasts from neurological disease donors and control donors. They used either glutamate or L-homocysteic acid as chemical substances that decreased cellular glutathione, and then tested four antioxidant substances to determine their effects on cell viability (see Figure 5 on page 109). The data of May and Gray Figures 1, 4 and 5 was measured as cell viability as determined by the trypan blue exclusion assay of Phillips (1973). **The Phillips (1973) assay has nothing to do with stress protein expression.** The assay simply measures whether cells are either alive or dead, **regardless of how**

cells may have died. For example, cells killed instantly by cyanide would also prove to be dead according to the trypan blue assay, although stress proteins would have had nothing to do with their death. The applicant has personally used this procedure. This assay lies outside the metes and bounds of the instant disclosure.

May and Gray have **nowhere** mentioned "stress protein expression" or "stress proteins," or the suppression thereof. So, they never studied the suppression of "stress protein expression." Yet the examiner has chosen to arbitrarily apply his own hindsight definitions and interpretation to the cited prior art. On page 3 of the USPTO letter in point 2 the examiner states:

> Furthermore they tested the control culture in the presence of a chemical **stress protein** [emphasis added]-inducing parameter with and without the agent. The chemical **stress protein** [emphasis added]-inducing parameter was 15mM L-HCA (see p. 108, first complete paragraph). This corresponds to claim 1(c)(5) and 1(c)(6). Finally, May et al. used **an indicator system capable of detecting stress protein expression** [emphasis added]. The indicator system was the percentage of cells which are viable; since cells die upon sufficient levels of **stress protein** [emphasis added] the viability assay corresponds to claim 1(d) as viability tests fairly anticipate use of an indicator system.

Actually, stress proteins have evolved to prevent cell death, not cause it. This hindsight description of the May and Gray procedure as being related to stress proteins is based entirely the opinion of the examiner and is nowhere supported in the cited prior art.

The applicant notes the statement of May and Gray (1985, page 102) that "these studies in conjunction with our subsequent investigations (May 1982) clearly indicate that control fibroblast cultures are susceptible to high levels of Glu and suggest that **a common toxic mechanism** [emphasis added] may be operative in both HD and control fibroblasts but initiated at lower Glu concentrations in HD cells." Hence, the prior art of May and Gray (1985) is clearly distinct from that of the present disclosure. In the method of the present disclosure, candidate drugs are selected that suppress stress protein expression preferentially in neurological disease fibroblasts, **but do not** suppress stress protein expression in control fibroblast cells **even when** said control cells are grown in the presence of a "stress protein-inducing parameter" (see Claim 1 of the instant disclosure). So, an ideal drug candidate of the instant disclosure would (1) suppress pre-existing levels of stress protein expression in neurological disease fibroblasts and (2) not suppress the induced level of stress proteins seen in control cells when grown in the presence of a stress protein-inducing parameter.

Also, as a matter of record, the following distinction regarding May and Gray should be noted. Besides measuring cell viability by the trypan blue assay, May and Gray also used an assay of "total glutathione content" to determine the toxic effect of glutamate (see Table 1) and the beneficial effects of

antioxidants (see Figure 2). Yet, glutathione is not a stress protein or a protein of any sort. In fact, it is a tripeptide of molecular weight 307.33 Daltons. That explains why the legend of May and Gray Table 1 mentions "total glutathione content was measured in **protein-free extracts** [emphasis added]..." and the legend of their Figure 2 mentions "total glutathione content was determined in **protein-free extracts** [emphasis added]." So, although they were measuring either decreases or increases in glutathione levels, this says nothing about stress protein expression.

On these grounds, reconsideration of the restriction requirement contained in the examiner's letter of mailing date 21 July 2005 is respectfully requested.

Based on the remarks noted above, the applicant maintains that there is no patentable distinction between the examiner's distinction of a Group (1) invention and the examiner's delineation of inventions of Groups (2) - (5). Solely in response to the requirement for election, applicant elects Group (1) with traverse.

Favorable action is earnestly solicited.

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Howard K. Shapiro, Ph.D.